



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 45/06, 31/44, A67K 31/40 // (A61K 31/44, 31:22) (A61K 31/40, 31:22)	A1	(11) International Publication Number: WO 98/00168 (43) International Publication Date: 8 January 1998 (08.01.98)
(21) International Application Number: PCT/EP97/03421 (22) International Filing Date: 1 July 1997 (01.07.97) (30) Priority Data: 96810436.4 2 July 1996 (02.07.96) DE (71) Applicant (for all designated States except US): NOVARTIS CONSUMER HEALTH S.A. [CH/CH]; Route de l'Etraz, CH-1260 Nyon (CH). (72) Inventors; and (75) Inventors/Applicants (for US only): TSCHOLLAR, Werner [DE/CH]; 127, rue de Lausanne, CH-1260 Nyon (CH). SCHMID, Beat [CH/CH]; Le Jordil, CH-1173 Féchy (CH). (74) Agent: ROTH, Bernhard, M.; Novartis AG, Patent- und Markenabteilung, Klybeckstrasse 141, CH-4002 Basel (CH).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: TOPICAL COMPOSITION COMPRISING A COMBINATION OF ANTIHISTAMINIC COMPOUNDS WITH TERPENOID COMPOUNDS (57) Abstract The invention relates to the topical use of an antihistaminic compound in combination with a terpenoid compound (for the manufacture of a topical medicament) for the treatment of allergic and inflammatory skin diseases, as well as to topical pharmaceutical compositions comprising a mixture of an antihistaminic compound with a terpenoid compound.		

BEST AVAILABLE COPY

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

TOPICAL COMPOSITION COMPRISING A COMBINATION OF ANTIHISTAMINIC COMPOUNDS WITH TERPENOID COMPOUNDS

The invention relates to the topical (= external) treatment of allergic and inflammatory skin diseases including atopic dermatitis with antihistaminic compounds as well as to novel topical pharmaceutical compositions comprising topically applicable antihistaminic compounds.

The topical application of antihistaminic compounds for the treatment of skin diseases, such as pruritus or insect bites, is known in the art.

It has now surprisingly been found that by topical application of an antihistaminic compound together with a terpenoid compound the efficacy of the combination is enhanced in an unexpected manner.

Therefore, the invention relates to the topical use of a topically applicable antihistaminic compound in combination with a terpenoid compound (for the manufacture of a topical medicament) for the treatment of allergic and inflammatory skin diseases.

Allergic and inflammatory skin diseases are, for example, pruritus, insect bites, sunburn, others burns, urticaria, eczema, neurodermitis, atopic dermatitis or contact dermatitis.

A topically applicable antihistaminic compound is especially a H1 receptor antagonist and is, for example, (a) an alkylamine derivative, e.g. acrivastine, bamipine, brompheniramine, chlorpheniramine, dexchlorpheniramine (= d-form of chlorpheniramine), dimethindene, Metron S, pheniramine, pyrrobutamine, thenaldine, tolpropamine or triprolidine; (b) an aminoalkyl ether, e.g. bietanautine, bromodiphenhydramine, carbinoxamine, clemastine, diphenylpyraline, doxylamine, embramine, medrylamine, mephenhydramine, p-methyl-diphenhydramine, orphenadrine, phenyltoloxamine, piprinhydrinate or setastine; (c) an ethylenediamine derivative, e.g. alloclamide, p-bromtripelennamine, chloropyramine, chlorothen, histapyrrodine, methafurylene, methaphenilene, methapyrilene, phenbenzamine, pyrilamine, talastine, thenyldiamine, thonzylamine hydrochloride, tripelennamine or zolamine; (d) a piperazine, e.g. cetirizine, chlorcyclizine, cinnarizine, clocinazine or hydroxyzine; (e) a phenothiazine tricyclic, e.g. ahistan, etymemazine,

fenethazine, N-hydroxyethylpromethazine chloride, isopromethazine, mequitazine, methdilazine, promethazine, pyrathiazine, thiazinamium methylsulfate or trimeprazine; (f) a tricyclic other than phenothiazines, e.g. azatadine, clobenzepam, cyproheptadine, depropine, isothipendyl, loratadine or prothipendyl; and (g) an antihistaminic compound of another structure, e.g. antazoline, astemizole, azelastine, cetoxime, clemizole, clobenztropine, diphenazoline, diphenhydramine, ebastine, emedastine, levocabastine, mebhydroline, phenindamine, terfenadine or tritoqualine.

The term "topically applicable antihistaminic compound" is to be understood as also to include (1) any topically acceptable salt of a free compound (acid or base) mentioned above, (2) any free compound (acid or base) or any other topically acceptable salt of a salt mentioned above, and (3) any active metabolite of a compound mentioned above. Examples for active metabolites are carebastine, which is the active metabolite of ebastine; norastemizole, which is the active metabolite of astemizole, or terfenadine carboxilate, which is the active metabolite of terfenadine.

A topically acceptable salt of an antihistaminic compound having a basic group is e.g. an acid addition salt. Suitable acid components may be, for example, strong inorganic acids, typically mineral acids, e.g. sulfuric acid, phosphoric acids, e.g. orthophosphoric acid, hydrohalic acids, e.g. hydrochloric acid, or strong organic carboxylic acids, typically lower alkanecarboxylic acids which may be substituted, e.g. by halogen, such as acetic acid or trifluoroacetic acid, dicarboxylic acids which may be unsaturated, e.g. oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, hydroxycarboxylic acids, e.g. ascorbic, glycolic, lactic, malic, tartaric or citric acid, amino acids, e.g. aspartic or glutaminic acid, or benzoic acid, or organic sulfonic acids, typically lower alkanesulfonic acids which may be substituted, e.g. by halogen, typically methanesulfonic acid, or arylsulfonic acids which may be substituted, e.g. by lower alkyl, typically p-toluenesulfonic acid.

A topically acceptable salt of an antihistaminic compound having an acidic group is e.g. an alkali metal or alkaline earth metal salt, e.g. the sodium, potassium, magnesium or calcium salt, an aluminium salt or a transition metal salt, e.g. the zinc or copper salt, or a corresponding salt with ammonia or organic amines. Organic amines that come into consideration are, for example, the following: alkylamines, such as mono-, di- or tri-lower alkylamines, e.g. ethylamine, tert-butylamine, diethylamine, diisopropylamine,

trimethylamine or triethylamine, alkylenediamines, such as lower alkylenediamines, e.g. ethylenediamine, alkylamines substituted by phenyl, such as mono- or di-phenyl-lower alkylamines, e.g. benzylamine or 1- or 2-phenylethylamine, hydroxy-alkylamines, such as mono-, di- or tri-hydroxy-lower alkylamines, e.g. mono-, di- or tri-ethanolamine or diisopropanolamine, oligohydroxy-lower alkylamines, e.g. tris-(hydroxymethyl)-methylamine, hydroxy-lower alkyl-di-lower alkylamines, e.g. N,N-dimethylamino- or N,N-diethylamino-ethanol, amino sugars, such as those in which the amino group is optionally substituted by at least one lower alkyl group, e.g. D-glucosamine, D-galactosamine or marmosamine (derived from monosaccharides in which an alcoholic hydroxy group is replaced by an amino group) or N-methyl-D-glucosamine (an N-lower alkylated amino sugar), cycloalkylamines, such as mono- or di-cycloalkylamines, e.g. cyclohexylamine or dicyclohexylamine, basic amino acids, e.g. arginine, histidine, lysine or ornithine, or cyclic amines, such as lower alkyleneamines or lower alkenyleneamines, e.g. azirine, pyrrolidine, 1-ethyl-pyrrolidine, 2-hydroxyethyl-pyrrolidine, piperidine, 1-ethyl-piperidine, 2-hydroxyethyl-piperidine or pyrroline, or lower alkyleneamines or lower alkenyleneamines in which the carbon chain is interrupted by aza (-NH-), N-lower alkylaza [-N(-lower alkyl)-], oxa (-O-) and/or thia (-S-), e.g. imidazoline, 3-methylimidazoline, piperazine, 4-methyl- or 4-ethylpiperazine, morpholine or thiomorpholine.

Preferred antihistaminic compounds are acrivastine, brompheniramine, chlorpheniramine, dexchlorpheniramine, dimethindene, triprolidine; bromodiphenhydramine, clemastine, phenyltoloxamine, piprinhydrate, pyrilamine, tripelennamine, cetirizine, hydroxyzine; methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, loratadine, astemizole, diphenhydramine, levocabastine and terfenadine, or topically acceptable salts thereof.

Particularly preferred antihistaminic compounds are dimethindene and clemastine, or a topically acceptable salt thereof, e.g. dimethindene maleate or clemastine hydrogen fumarate.

A terpenoid compound is, for example, a monoterpenoid compound, a diterpenoid compound, a triterpenoid compound or a sesquiterpenoid compound.

A monoterpenoid compound is e.g. camphor, 3-carene, carvacrol, carvone, chrysanthemic acid; cineol, e.g. 1,8-cineol; gefarnate, geraniol, linalool, limonene, menthol, pulegone, thujone or thymol.

A diterpenoid compound is e.g. aphidicolin, forskolin, phytanic acid or phytol.

A triterpenoid compound is, for example, glycyrrhetic acid or a sapogenin, e.g. oleanolic acid or diosgenin.

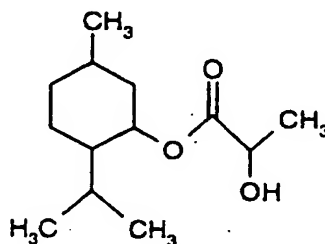
A sesquiterpenoid compound is e.g. farnesol or santonin.

The term "terpenoid compound" is intended also to cover any derivative and any topically acceptable salt of a terpenoid compound. Preferred derivatives of a terpenoid compound having one or more hydroxy groups are those wherein one or more of the hydroxy groups are esterified by a carboxylic acid (= terpenoid compound esters).

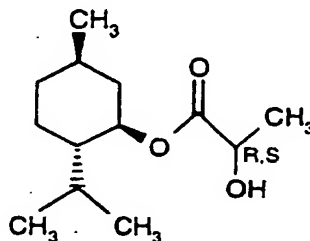
A carboxylic acid is, for example, a C₁-C₇-aliphatic, a cycloaliphatic, an aromatic, an aromatic-C₁-C₇-aliphatic, a heteroaromatic or a heteroaromatic-C₁-C₇-aliphatic carboxylic acid, which carboxylic acid may be unsubstituted or substituted, for example by one or more substituents selected from hydroxy, halogen, C₁-C₇-alkoxy, carboxy, C₁-C₇-alkoxycarbonyl, cyano, amino, C₁-C₇-alkylamino, di-C₁-C₇-alkylamino, C₁-C₇-alkanoylamino, nitro, C₁-C₇-alkyl and halogen-C₁-C₇-alkyl (e.g. trifluoromethyl). More especially, a carboxylic acid is a C₁-C₇-alkanoic acid which is unsubstituted or substituted by hydroxy, halogen, carboxy or amino, a C₃-C₇-cycloalkanoic acid; a phenyl-C₁-C₇-alkanoic acid, a benzoic acid or a naphthoic acid in each of which the phenyl ring(s) may be unsubstituted or substituted by one or more substituents selected from C₁-C₇-alkyl, halogen-C₁-C₇-alkyl, hydroxy, halogen, C₁-C₇-alkoxy, carboxy, C₁-C₇-alkoxycarbonyl, cyano, amino, C₁-C₇-alkylamino, di-C₁-C₇-alkylamino, C₁-C₇-alkanoylamino and nitro; or a heteroaromatic carboxylic acid or a heteroaromatic-C₁-C₇-alkanoic acid in each of which the heteroaromate is selected from furan optionally substituted by C₁-C₇-alkyl or halogen, thiophene optionally substituted by C₁-C₇-alkyl or halogen and pyridine optionally substituted by hydroxy, lower alkoxy, trifluoromethyl, cyano or C₁-C₇-alkyl. In particular, a carboxylic acid is a C₁-C₇-alkanoic acid which is unsubstituted or substituted by hydroxy.

Preferred terpenoid compounds are menthol, menthol esters, especially menthyl lactate, or cineol, more preferably menthol or menthyl lactate, and in one embodiment menthol, and in another embodiment menthyl lactate.

The structural formula of menthyl lactate is as follows:



As the compound contains 4 asymmetric carbon atoms, there are existing 16 different stereoisomers. The term "menthyl lactate" is intended to cover each of these stereoisomers as well as any racemates and any other mixtures of these stereoisomers. Preferred is the racemate of the following structure



which is derived from the naturally occurring (-)-menthol. This compound is available commercially e.g. from Haarmann & Reimer GmbH (Germany) under the name FRESCOLAT, Type ML. It can also be readily made by processes known in the art by esterifying the hydroxy group of menthol with lactic acid.

The combination according to the invention can be applied, usually in the form of a topical pharmaceutical composition, to any portion of the skin. However, application to the external genitalia, or the eyelids, or lips is not suggested, recommended, or usually desired.

It has surprisingly been found that by combining an antihistaminic compound with a terpenoid compound in a pharmaceutical composition for topical administration the antiallergic and antiinflammatory efficacy of the combination is enhanced in an unexpected manner. The antihistaminic compound and the terpenoid compound both act as topical antiinflammatory agents but have different mechanisms of action and therefore act complementarily. Moreover, the topical compositions of the invention are characterised by an extremely good skin permeation of the drugs applied.

The topical pharmaceutical compositions of the invention have valuable pharmacological properties. Especially they are beneficial in the treatment of allergic and inflammatory skin diseases including atopic dermatitis.

The beneficial properties of the combinations of the invention can be demonstrated, for example, in the following tests.

(1) Itch threshold to intracutaneous histamine and the "wheal and flare" reaction after intracutaneous injection of histamine in human volunteers [see Lever et al., Pharmacol. 4 (1991) 109-112].

(2) Carrageenin-induced edema in hind paw of the rat as an assay for antiinflammatory drugs [Winter et al., Proc. Soc. Exp. Biol. Med. 111 (1962) 544-547].

(3) Inflammation induced with croton oil in the mouse ear [Tonelli et al., Endocrinology 77 (1965) 625-634].

(4) Model of intradermal histamine challenge in unanesthetized hairless rats [M. Harada et al., J. Pharm. Pharmacol. 23 (1971) 218]: In this test, the test substances are topically applied to the abdominal skin of the animals. Then, after 0.5 h, they are removed, a tracer dye is intravenously injected and challenge with intradermal histamine (0, 25, 50, 75, 100, 200 and 400 nmol/site) is performed within the treated zones. Efficacy is assessed by comparison between the amount of dye liberated from the blood vessels in treated versus untreated areas of skin. When comparing a gel containing 0.1% of dimethindene maleate and 4.0% of menthol with an analogous gel containing 0.1% of dimethindene maleate only,

the dermal inflammation induced by histamine is reduced in a statistically significant manner ($p < 0.05$) by the combination only.

The safety of the compositions of the invention is confirmed by classical toxicological studies, such as the acute toxicity mice test, the acute rabbit skin/eye irritation test or sensitization tests. Adverse effects, such as rough skin or skin irritation, are not observed.

In particular, the invention relates to the use of a mixture of an antihistaminic compound with a terpenoid compound, in which mixture the antihistaminic compound is present in an amount of from 0.01 up to 15%, and the terpenoid compound is present in an amount of from 0.1 up to 15%, especially of from 0.1 up to 10%, very especially of from 0.5 up to 10%, more especially of from 0.5 up to 8%, most especially of from 1 up to 8%, advantageously of from 2 up to 8%, in particular of from 3 up to 8%, and first and foremost of from 4 up to 8%; further of from 3 up to 10%.

Normally, the combination of an antihistaminic compound and a terpenoid compound is used in the form of a topical pharmaceutical composition which is also an object of the present invention.

Thus the invention further relates to a topical pharmaceutical composition comprising at least one topically applicable antihistaminic compound and at least one terpenoid compound together with at least one topically acceptable carrier material.

Preferably, the topically administered pharmaceutical compositions according to the invention comprise both the topically applicable antihistaminic compound(s) and the terpenoid compound in pharmacologically effective amounts.

The daily dosage of the active ingredients depends on age and individual condition and on the mode of administration. For example, the topical pharmaceutical compositions, for example in the form of emulsion-gels, creams or ointments, may be applied once, twice or three times daily. But also more frequent daily applications are possible: such can provide a continual therapy which may lead to an even more rapid improvement of the conditions treated. Patches and bandages may be applied, for example, once daily or only once, twice or three times a week.

In a topical composition of the invention - as well in a mixture used according to the invention - the antihistaminic compound(s) is (are) e.g. present in an amount of from 0.01 up to 15%, especially of from 0.02 up to 5%, and in particular of from 0.02 up to 2.5%, of the total composition.

In a topical composition of the invention, the terpenoid compound is present in an amount of from 0.1 up to 15%, especially of from 0.1 up to 10%, very especially of from 0.5 up to 10%, more especially of from 0.5 up to 8%, most especially of from 1 up to 8%, advantageously of from 2 up to 8%, in particular of from 3 up to 8%, and first and foremost of from 4 up to 8%; further of from 3 up to 10%.

The dosage of the active ingredients may depend on various factors, such as warm-blooded species, sex, age, weight and individual condition of the warm-blooded animal.

Moreover, the invention relates to a method of treating allergic and inflammatory skin diseases which comprises topically administering to a mammal in need of such treatment a therapeutically effective amount of at least one antihistaminic compound together with a therapeutically effective amount of at least one terpenoid compound.

Pharmaceutical compositions suitable for topical administration are e.g. creams, lotions, ointments, microemulsions, fatty ointments, gels, emulsion-gels, pastes, foams, tinctures, solutions, patches, bandages and transdermal therapeutic systems; preferred are emulsion-gels, gels, creams, lotions, solutions, patches and bandages.

Creams or lotions are oil-in-water emulsions. As oily base there are used especially fatty alcohols, especially those containing from 12 to 18 carbon atoms, for example lauryl, cetyl or stearyl alcohol, fatty acids, especially those containing from 10 to 18 carbon atoms, for example palmitic or stearic acid, fatty acid esters, e.g. glyceryl tricaprilcaprate (neutral oil) or cetyl palmitate, liquid to solid waxes, for example isopropyl myristate, wool wax or beeswax, and/or hydrocarbons, especially liquid, semi-solid or solid substances or mixtures thereof, for example petroleum jelly (petrolatum) or paraffin oil. Suitable emulsifiers are surface-active substances having predominantly hydrophilic properties, such as corresponding non-ionic emulsifiers, for example fatty acid esters of polyalcohols and/or

ethylene oxide adducts thereof, especially corresponding fatty acid esters with (poly)ethylene glycol, (poly)propylene glycol or sorbitol, the fatty acid moiety containing especially from 10 to 18 carbon atoms, especially partial glycerol fatty acid esters or partial fatty acid esters of polyhydroxyethylene sorbitan, such as polyglycerol fatty acid esters or polyoxyethylene sorbitan fatty acid esters (Tweens), and also polyoxyethylene fatty alcohol ethers or fatty acid esters, the fatty alcohol moiety containing especially from 12 to 18 carbon atoms and the fatty acid moiety especially from 10 to 18 carbon atoms, such as polyhydroxyethylenecetylstearyl ether (for example Cetomacrogol 1000) or polyhydroxyethyleneglycerol fatty acid ester (for example Tagat S), or corresponding ionic emulsifiers, such as alkali metal salts of fatty alcohol sulfates, especially having from 12 to 18 carbon atoms in the fatty alcohol moiety, for example sodium lauryl sulfate, sodium cetyl sulfate or sodium stearyl sulfate, which are usually used in the presence of fatty alcohols, for example cetyl alcohol or stearyl alcohol. Additives to the aqueous phase are, inter alia, agents that prevent the creams from drying out, for example humectants, such as polyalcohols, such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, and also preservatives, perfumes, gelling agents, etc..

Ointments are water-in-oil emulsions that contain up to 70%, but preferably from approximately 20% to approximately 50%, water or aqueous phase. Suitable as fatty phase are especially hydrocarbons, for example petroleum jelly, paraffin oil and/or hard paraffins, which, in order to improve the water-binding capacity, preferably contain suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, or wool wax or beeswax. Emulsifiers are corresponding lipophilic substances, for example of the type indicated above, such as sorbitan fatty acid esters (Spans), for example sorbitan oleate and/or sorbitan isostearate. Additives to the aqueous phase are, inter alia, humectants, such as polyalcohols, for example glycerol, propylene glycol, sorbitol and/or polyethylene glycol, and also preservatives, perfumes, etc.

Microemulsions are isotropic systems based on the following four components: water, a surfactant, for example a tensioactive, a lipid, such as a non-polar or polar oil, for example paraffin oil, and an alcohol or polyalcohol containing lipophilic groups, for example 2-octyldodecanol or ethoxalated glycerol or polyglycerol esters. If desired, other additives may be added to the microemulsions.

Fatty ointments are water-free and contain as base especially hydrocarbons, for example paraffin, petroleum jelly and/or liquid paraffins, also natural or partially synthetic fat, such as fatty acid esters of glycerol, for example coconut fatty acid triglyceride, or preferably hardened oils, for example hydrogenated groundnut oil, castor oil or waxes, also fatty acid partial esters of glycerol, for example glycerol mono- and di-stearate, and also, for example, the fatty alcohols increasing the water-absorption capacity, emulsifiers and/or additives mentioned in connection with the ointments.

With gels, a distinction is made between aqueous gels, water-free gels and gels having a low water content, which gels consist of swellable, gel-forming materials. There are used especially transparent hydrogels based on inorganic or organic macromolecules. High molecular weight inorganic components having gel-forming properties are predominantly water-containing silicates, such as aluminium silicates, for example bentonite, magnesium aluminium silicates, for example Veegum, or colloidal silicic acid, for example Aerosil. As high molecular weight organic substances there are used, for example, natural, semi-synthetic or synthetic macromolecules. Natural and semi-synthetic polymers are derived, for example, from polysaccharides containing a great variety of carbohydrate components, such as celluloses, starches, tragacanth, gum arabic and agar-agar, and gelatin, alginic acid and salts thereof, for example sodium alginate, and derivatives thereof, such as lower alkylcelluloses, for example methyl- or ethyl-cellulose, carboxy- or hydroxy-lower alkylcelluloses, for example carboxymethyl- or hydroxyethyl-cellulose. The components of synthetic gel-forming macromolecules are, for example, suitably substituted unsaturated aliphatic compounds such as vinyl alcohol, vinylpyrrolidine, acrylic or methacrylic acid. Examples of such polymers are polyvinyl alcohol derivatives, such as polyviol, polyvinylpyrrolidines, such as collidone, polyacrylates and polymethacrylates, especially having a molecular weight of from approximately 80000 to approximately 1 million, or salts thereof, such as Rohagit S, Eudispert or Carbopol (Carbomer). Customary additives, such as preservatives, humectants or perfumes, may be added to the gels.

Emulsion-gels - also called "emulgels" - represent topical compositions which combine the properties of a gel with those of an oil-in-water emulsion. In contrast to gels, they contain a lipid phase which due to its fat-restoring properties enables the formulation to be massaged in whilst, at the same time, the direct absorption into the skin is experienced as a pleasant

property. Furthermore, one can observe an increased solubility for lipophilic active ingredients. One advantage of emulsion-gels over oil-in-water emulsions resides in the enhanced cooling effect which is brought about by the coldness due to evaporation of the additional alcohol component, if present. Furthermore, one can observe an improved solubility of polar active ingredients.

Foams are administered, for example, from pressurised containers and are liquid oil-in-water emulsions in aerosol form; unsubstituted hydrocarbons, such as alkanes, for example propane and/or butane, are used as propellant. As oil phase there are used, inter alia, hydrocarbons, for example paraffin oil, fatty alcohols, for example cetyl alcohol, fatty acid esters, for example isopropyl myristate, and/or other waxes. As emulsifiers there are used, inter alia, mixtures of emulsifiers having predominantly hydrophilic properties, such as polyoxyethylene sorbitan fatty acid esters (Tweens), and emulsifiers having predominantly lipophilic properties, such as sorbitan fatty acid esters (Spans). The customary additives, such as preservatives, etc., are also added.

Tinctures and solutions generally have an ethanolic base, to which water may be added and to which there are added, inter alia, polyalcohols, for example glycerol, glycols and/or polyethylene glycol, as humectants for reducing evaporation, and fat-restoring substances, such as fatty acid esters with low molecular weight polyethylene glycols, propylene glycol or glycerol, that is to say lipophilic substances that are soluble in the aqueous mixture, as a replacement for the fatty substances removed from the skin by the ethanol, and, if necessary, other adjuncts and additives. Suitable tinctures or solutions may also be applied in spray form by means of suitable devices.

Transdermal therapeutic systems with - in particular - local delivery of the active substances contain an effective amount of each of the active ingredients optionally together with a carrier. Useful carriers comprise absorbable pharmacological suitable solvents to assist passage of the active ingredients through the skin. Transdermal delivery systems are, for example, in the form of a patch comprising (a) a substrate (= backing layer or film), (b) a matrix containing the active ingredients, optionally carriers and optionally (but preferably) a special adhesive for attaching the system to the skin, and normally (c) a protection foil (= release liner). The matrix (b) is normally present as a mixture of all components or may consist of separate layers.

The manufacture of the topically administrable pharmaceutical preparations is effected in a manner known per se, for example by dissolving or suspending the active ingredients in the base or, if necessary, in a portion thereof. When the active ingredients are administered in the form of a solution, they are generally dissolved in one of the two phases before emulsification.

The following examples are intended to illustrate the invention.

Example 1: An emulsion-gel containing the maleate salt of dimethindene and menthyl lactate is manufactured as follows.

Composition

(a) dimethindene maleate	0.1% by weight
(b) menthyl lactate	6.0% by weight
(c) isopropanol	20.0% by weight
(d) polyethylene glycol 300	3.0% by weight
(e) polyhydroxyethylene cetyl stearyl ether (Cetomacrogol 1000)	2.0% by weight
(f) paraffin oil, viscous	2.5% by weight
(g) Mygliol® 812 [= a neutral oil (caprilo/capric triglyceride)]	2.5% by weight
(h) acrylic acid polymerisate (Carbopol® 934 P)	1.0% by weight
(i) diethylamine	0.7% by weight
(j) sodium sulphite	0.1% by weight
(k) water, demineralised	to make up to 100% by weight

The acrylic acid polymerisate is dispersed in a portion of water by means of a rotor-stator homogeniser (for example Homorex®). A solution of the maleate salt of dimethindene, diethylamine, sodium sulphite and polyethylene glycol 300 in isopropanol and the remaining water is added thereto and distributed homogeneously. To form the fatty phase, the polyhydroxyethylene cetyl stearyl ether, Mygliol® 812 and the paraffin oil are melted together at 75°. Menthyl lactate is added to the fatty phase, and then the whole fatty phase is slowly added to the previously formed gel and emulsified.

Example 2: An emulsion-gel containing the maleate salt of dimethindene and menthyl lactate is manufactured as follows.

Composition

(a) dimethindene maleate	0.1% by weight
(b) menthyl lactate	6.0% by weight
(c) propylene glycol	15.0% by weight
(d) polyhydroxyethylene cetyl stearyl ether (Cetomacrogol 1000)	2.0% by weight
(e) paraffin oil, viscous	2.5% by weight
(f) Mygliol® 812	2.5% by weight
(g) acrylic acid polymerisate (Carbopol® 934 P)	1.0% by weight
(h) sodium hydroxide	0.3% by weight
(i) butylhydroxytoluene	0.02% by weight
(j) disodium edetate	0.05% by weight
(k) benzyl alcohol	0.5% by weight
(l) benzalkonium chloride	0.01% by weight
(m) water, demineralised	to make up to 100% by weight

The acrylic acid polymerisate is dispersed in a portion of water by means of a rotor-stator homogeniser (for example Homorex®). A solution of dimethindene maleate, NaOH, butylhydroxytoluene, disodium edetate and benzalkonium chloride in a mixture of propylene glycol/water is added thereto and distributed homogeneously. To form the fatty phase, the polyhydroxyethylene cetyl stearyl ether, Mygliol® 812, the paraffin oil and benzyl alcohol are melted together at 75°. The menthyl lactate is added to the fatty phase, and then the whole fatty phase is slowly added to the previously formed gel and emulsified.

Example 3: An emulsion-gel containing the maleate salt of dimethindene and l-menthol has the following composition and is manufactured in analogy to the examples 1 and 2.

Composition

(a) dimethindene maleate	0.1% by weight
--------------------------	----------------

(b) l-menthol	4.0% by weight
(c) caprylic/capric acid esters of saturated fatty alcohols (Cetiol® LC)	2.5% by weight
(d) paraffin oil, viscous	2.5% by weight
(e) polyhydroxyethylene cetyl stearyl ether (Cetomacrogol 1000)	2.0% by weight
(f) propylene glycol	15.0% by weight
(g) disodium edetate dihydrate	0.05% by weight
(h) benzalkonium chloride	0.01% by weight
(i) benzyl alcohol	0.5% by weight
(j) butylhydroxytoluene	0.02% by weight
(k) sodium hydroxide	0.12% by weight
(l) acrylic acid polymerisate (Carbomer® 974 P)	0.4% by weight
(m) water, purified	to make up to 100% by weight

Example 4: A lotion containing the maleate salt of dimethindene and menthyl lactate has the following composition and is manufactured in analogy to the examples 1 and 2.

Composition

(a) dimethindene maleate	0.1% by weight
(b) menthyl lactate	6.0% by weight
(c) propylene glycol	15.0% by weight
(d) polyhydroxyethylene cetyl stearyl ether (Cetomacrogol 1000)	2.0% by weight
(e) paraffin oil, viscous	2.5% by weight
(f) Mygliol® 812	2.5% by weight
(g) acrylic acid polymerisate (Carbopol® 934 P)	0.3% by weight
(h) sodium hydroxide	0.1% by weight
(i) butylhydroxytoluene	0.02% by weight
(j) disodium edetate	0.05% by weight
(k) benzyl alcohol	0.5% by weight
(l) benzalkonium chloride	0.01% by weight
(m) water, demineralised	to make up to 100% by weight

Example 5: An emulsion-gel containing clemastine hydrogen fumarate and menthyl lactate is manufactured as follows.

Composition

(a) clemastine hydrogen fumarate	0.04% by weight
(b) menthyl lactate	6.0% by weight
(c) isopropanol	20.0% by weight
(d) polyethylene glycol 300	3.0% by weight
(e) polyhydroxyethylene cetyl stearyl ether (Cetomacrogol 1000)	2.0% by weight
(f) paraffin oil, viscous	2.5% by weight
(g) Mygliol® 812	2.5% by weight
(h) acrylic acid polymerisate (Carbopol® 934 P)	1.0% by weight
(i) diethylamine	0.7% by weight
(j) sodium sulphite	0.1% by weight
(k) water, demineralised	to make up to 100% by weight

The acrylic acid polymerisate is dispersed in a portion of water by means of a rotor-stator homogeniser (for example Homorex®). A solution of clemastine hydrogen fumarate, diethylamine, sodium sulphite and polyethylene glycol 300 in isopropanol and the remaining water is added thereto and distributed homogeneously. To form the fatty phase, the polyhydroxyethylene cetyl stearyl ether, Mygliol® 812 and the paraffin oil are melted together at 75°. Menthyl lactate is added to the fatty phase, and then the whole fatty phase is slowly added to the previously formed gel and emulsified.

Claims

1. Use of a topically applicable antihistaminic compound in combination with a terpenoid compound for the manufacture of a topical medicament for the treatment of allergic and inflammatory skin diseases.
2. Use according to claim 1, where the topically applicable antihistaminic compound drug is selected from acrivastine, brompheniramine, chlorpheniramine, dexchlorpheniramine, dimethindene, triprolidine; bromodiphenhydramine, clemastine, phenyltoloxamine, piprinhydrinate, pyrilamine, tripeleminamine, cetirizine, hydroxyzine; methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, loratadine, astemizole, diphenhydramine, levocabastine and terfenadine, and topically acceptable salts thereof.
3. Use according to claim 1, where the topically applicable antihistaminic compound drug is selected from dimethindene, clemastine and topically applicable salts thereof.
4. Use according to any one of claims 1 to 3, where the terpenoid compound is selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid; cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thujone, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetic acid, a sapogenin selected from oleanolic acid and diosgenin, farnesol and santonin; wherein any hydroxy group present may be in free form or esterified by a carboxylic acid; and topically acceptable salts thereof, for the manufacture of a topical medicament for the treatment of allergic and inflammatory skin diseases.
5. Use according to any one of claims 1 to 3, where the terpenoid compound is selected from menthol, menthol esters and cineol.
6. Use according to any one of claims 1 to 3, where the terpenoid compound is selected from menthol and menthyl lactate.
7. Use of a topically applicable antihistaminic compound in combination with a terpenoid compound according to any one of claims 1 to 6, where the topically applicable antihistaminic compound is present in an amount of from 0.01 up to 15% and the terpenoid

compound is present in an amount of from 0.1 up to 15% in the topical medicament manufactured.

8. Use of a topically applicable antihistaminic compound in combination with a terpenoid compound according to any one of claims 1 to 6, where the topically applicable antihistaminic compound is present in an amount of from 0.02 up to 5% and the terpenoid compound is present in an amount of from 2 up to 8% in the topical medicament manufactured.

9. A topical pharmaceutical composition comprising at least one topically applicable antihistaminic compound and at least one terpenoid compound together with at least one topically acceptable carrier material.

10. A topical pharmaceutical composition according to claim 9, wherein the topically applicable antihistaminic compound drug(s) is (are) selected from acrivastine, brompheniramine, chlorpheniramine, dexchlorpheniramine, dimethindene, triprolidine; bromodiphenhydramine, clemastine, phenyltoloxamine, piprinhydrinate; pyrilamine, tripelemnamine, cetirizine, hydroxyzine; methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, loratadine, astemizole, diphenhydramine, levocabastine and terfenadine, and topically acceptable salts thereof.

11. A topical pharmaceutical composition according to claim 9, wherein the topically applicable antihistaminic compound drug(s) is (are) selected from acrivastine, brompheniramine, dimethindene, triprolidine; bromodiphenhydramine, clemastine, phenyltoloxamine, piprinhydrinate, pyrilamine, tripelemnamine, cetirizine, hydroxyzine; methdilazine, promethazine, trimeprazine, azatadine, cyproheptadine, loratadine, astemizole, diphenhydramine, levocabastine and terfenadine, and topically acceptable salts thereof,

wherein the terpenoid compound(s) is (are) selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid; cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thujone, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetic acid, a sapogenin selected from oleanolic acid and diosgenin, farnesol and

santonin; in which terpenoid compound any hydroxy group present may be in free form or esterified by a carboxylic acid; and topically acceptable salts thereof;

which topical pharmaceutical composition does not contain a corticosteroid, a higher alcohol phosphate anionic surfactant, methyl salicylate, vitamin E, an ester or amide of a monocarboxylic acid said monocyclic acid having 5 to 19 carbon atoms, cocaine and novacaine, and

which topical pharmaceutical composition does not contain a drug carrier in the form of a fat emulsion which contains the drug(s) and has a mean particle diameter of less than 200 nm.

12. A topical pharmaceutical composition according to claim 9, wherein the topically applicable antihistaminic compound drug(s) is (are) selected from dimethindene, clemastine and topically applicable salts thereof.

13. A topical pharmaceutical composition according to any one of claims 9 to 12, wherein the terpenoid compound(s) is (are) selected from the group consisting of camphor, 3-carene, carvacrol, carvone, chrysanthemic acid; cineol, gefarnate, geraniol, linalool, limonene, menthol, pulegone, thujone, aphidicolin, forskolin, phytanic acid, phytol, glycyrrhetic acid, a sapogenin selected from oleanolic acid and diosgenin, farnesol and santonin; in which terpenoid compound any hydroxy group present may be in free form or esterified by a carboxylic acid; and topically acceptable salts thereof.

14. A topical pharmaceutical composition according to any one of claims 9 to 12, where the terpenoid compound is selected from menthol, menthol esters or cineol.

15. A topical pharmaceutical composition according to any one of claims 9 to 12, where the terpenoid compound is selected from menthol or menthyl lactate.

16. A topical pharmaceutical composition according to any one of claims 9 to 15, wherein the topically applicable antihistaminic compound(s) is (are) present in an amount of from 0.01 up to 15% and the terpenoid compound is present in an amount of from 0.1 up to 15%.

17. A topical pharmaceutical composition according to any one of claims 9 to 15, wherein the topically applicable antihistaminic compound(s) is (are) present in an amount of from 0.02 up to 5% and the terpenoid compound is present in an amount of from 2 up to 8%.
18. A topical pharmaceutical composition according to claim 14 or claim 15, wherein the topically applicable antihistaminic compound(s) is (are) present in an amount of from 0.02 up to 5% and the terpenoid compound is present in an amount of from 3 up to 10%.
19. A topical pharmaceutical composition according to any one of claims 9 to 18, which is in the form of an emulsion-gel, a gel, a cream, a lotion, a solution, a patch or a bandage.
20. A method of treating allergic or inflammatory skin diseases, which comprises topically administering to a mammal in need of such treatment a therapeutically effective amount of an antihistaminic compound together with a therapeutically effective amount of a terpenoid compound.

INTERNATIONAL SEARCH REPORT

BEST AVAILABLE COPY

Inter. Application No
PCT/EP 97/03421

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06 A61K31/44 A61K31/40 //(A61K31/44,31:22),
(A61K31/40,31:22)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 9348 Derwent Publications Ltd., London, GB; AN 93-383002 XP002021800 & JP 05 286 860 A (KOWA CO LTD) see abstract	1,2, 4-10, 13-20
X	--- PATENT ABSTRACTS OF JAPAN vol. 012, no. 059 (C-478), 23 February 1988 & JP 62 205019 A (KAO CORP), 9 September 1987, see abstract --- -/-	1,2, 4-10, 13-20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *Z* document member of the same patent family

Date of the actual completion of the international search

8 September 1997

Date of mailing of the international search report

26. 09. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Kanbier, D

. INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/EP 97/03421

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI Week 9228 Derwent Publications Ltd., London, GB; AN 92-230523 XP002021801 & JP 04 154 719 A (KIKUCHI H) , 27 May 1992 see abstract</p> <p style="text-align: center;">---</p>	<p>1,2, 4-10, 13-20</p>
X	<p>EP 0 158 090 A (R. ISMAIL) 16 October 1985</p> <p style="text-align: center;">---</p>	<p>1-4,9, 10,12, 13,19,20</p>
A	<p>see page 5, paragraph 5 - page 6, paragraph 2; claims 1,8,15,19; examples 98,136 see page 7, paragraph 2-3 see page 11, paragraph 4 - page 12, paragraph 1; example 114</p> <p style="text-align: center;">---</p>	<p>5,6</p>
X	<p>WO 94 08550 A (PROCTER & GAMBLE) 28 April 1994 see page 8-11; claims 1,4,12-14 see page 2, paragraph 6 - page 3, paragraph 1</p> <p style="text-align: center;">---</p>	<p>1,4-17, 19,20</p>
X	<p>WO 91 12010 A (DERMATOLOGIC RESEARCH CORPORATION) 22 August 1991</p> <p style="text-align: center;">---</p>	<p>1,2,4-6, 9,10, 13-15, 19,20</p>
A	<p>see page 1, line 15 - page 2, line 10 see page 4, paragraph 1; claims 3,4</p> <p style="text-align: center;">---</p>	<p>7,8</p>
X	<p>PATENT ABSTRACTS OF JAPAN vol. 008, no. 241 (C-250), 6 November 1984 & JP 59 122420 A (OOTSUKA SEIYAKU KOUJIYU KK), 14 July 1984, see abstract</p> <p style="text-align: center;">---</p>	<p>9,10</p>
X	<p>WO 92 13540 A (G. PARENT) 20 August 1992 see page 3-4; claim 4</p> <p style="text-align: center;">---</p>	<p>9,10,19, 20</p>
X	<p>WO 89 12626 A (HERMAN STEPHEN) 28 December 1989 see page 11; claims 1-6,8,9,12,14,18-20</p> <p style="text-align: center;">---</p>	<p>1,4,9, 11,13, 19,20</p>
A	<p>EP 0 315 079 A (NIPPON SHINYAKU COMPANY) 10 May 1989 see page 4, line 33 - page 4, line 23</p> <p style="text-align: center;">-----</p>	<p>2,4,5,9, 10,13, 14,19,20</p>

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 20

because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Remark : Although claim 20 is directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No.
PCT/EP 97/03421

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 158090 A	16-10-85	DE 3410641 A	24-10-85
		DE 3441711 A	15-05-86
		DE 3504695 A	14-08-86
		CA 1257200 A	11-07-89
		DE 3507791 A	26-09-85
		DE 3522572 A	02-01-87
		DE 3586859 A	07-01-93
		EP 0343694 A	29-11-89
		US 4938960 A	03-07-90
		US 5652261 A	29-07-97
		US 5541220 A	30-07-96
		JP 61040210 A	26-02-86

WO 9408550 A	28-04-94	AU 5134893 A	09-05-94
		AU 678561 B	05-06-97
		AU 4930793 A	09-05-94
		EP 0662840 A	19-07-95
		JP 8502288 T	12-03-96

WO 9112010 A	22-08-91	US 5057500 A	15-10-91
		AU 7325991 A	03-09-91
		CA 2074493 A	13-08-91
		CA 2074493 C	03-10-95
		EP 0515517 A	02-12-92
		JP 2554419 B	13-11-96
		JP 5502677 T	13-05-93
		KR 9514448 B	28-11-95

WO 9213540 A	20-08-92	AU 1183092 A	07-09-92

WO 8912626 A	28-12-89	AU 4058689 A	12-01-90
		CA 1338083 A	27-02-96
		EP 0427781 A	22-05-91
		JP 4502145 T	16-04-92
		US 5364879 A	15-11-94
		US 4983637 A	08-01-91
		US 5086076 A	04-02-92
		US 5126376 A	30-06-92
		US 5190977 A	02-03-93
		US 5270344 A	14-12-93

BEST AVAILABLE COPY

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 97/03421

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 8912626 A		US 5190979 A	02-03-93
		US 5260342 A	09-11-93
EP 315079 A	10-05-89	AT 119031 T	15-03-95
		AU 2447288 A	04-05-89
		BE 1001760 A	27-02-90
		CA 1333993 A	17-01-95
		CH 677605 A	14-06-91
		CN 1042080 A	16-05-90
		DE 3853191 D	06-04-95
		DE 3853191 T	19-10-95
		FR 2622442 A	05-05-89
		GB 2211408 A,B	05-07-89
		JP 2000203 A	05-01-90
		JP 7098740 B	25-10-95
		KR 9613281 B	02-10-96
		NL 8802657 A	16-05-89
		US 5651991 A	29-07-97

BEST AVAILABLE COPY

THIS PAGE BLANK (CPTO)